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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,589	08/18/2003	Debra D. Pittman	WYTH-P01-002	3988

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EXAMINER	
EMCH, GREGORY S	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,589	PITTMAN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *33-41 and 45-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 8-31 and 42-44* is/are rejected.

7)☒ Claim(s) *3-7 and 32* is/are objected to.

8)☒ Claim(s) *1-84* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/1/04; 11/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election of Group I, claims 1-32 and 42-44, in the reply filed on 24 August 2006 is acknowledged. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 33-41 and 45-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 1-32 and 42-44 are under examination in the instant office action.

Information Disclosure Statements

Signed and initialed copies of the IDS papers filed 01 March 2004 and 25 November 2005 are enclosed in this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: There is no signature for Applicant Glenn Larson.

Claim Objections

Claims 3-7 and 32 are objected to because of the following informalities:

The claims refer to sequences set forth in Applicants' sequence listing. 37 CFR 1.821 (d) states, "Where the description or claims of a patent application discuss a sequence that is set forth in the 'Sequence Listing' in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by 'SEQ ID NO:' in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Appropriate corrections are required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 8-31 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112,

¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are directed to a fusion protein comprising a Receptor for Advanced Glycation End Product Ligand Binding Element (RAGE-LBE) and an immunoglobulin element, further comprising a dimerizing polypeptide (including an amphiphilic polypeptide), a purification polypeptide, a stabilizing polypeptide, or a targeting polypeptide, as well as a TNF-α inhibitor, and associated pharmaceutical compositions and protein complexes.

The specification discloses that a Receptor for Advanced Glycation End Products Ligand Binding Element (RAGE-LBE) includes any extracellular portion of a transmembrane RAGE polypeptide and fragments thereof that retain the ability to bind a RAGE ligand (p.12, lines 10-13). Further, pharmaceutical compositions of the present invention include those that comprise a TNF-α inhibitor selected from the group consisting of a small molecule, an antibody, a peptidomimetic, and a TNFRII-Fc fusion protein (p.5, lines 14-20). Also, etanercept and infliximab are disclosed as examples of anti-TNF agents (p.42, line 4). In addition, the term "dimerizing polypeptide" or "dimerizing domain" is defined as any polypeptide that forms a dimer or multimer with another polypeptide. A few examples are disclosed, i.e., an amphiphilic polypeptide, an IgG Fc element that forms homomultimers and the Jun and Fos leucine zipper domains that form heteromultimers with each other (p.10, lines 16-25 and p.18, lines 7-16).

Claims 1, 2, 8-31 and 42-44 are genus claims because the specification (and claims) do not set forth the structure of the multitude of RAGE-LBE's, TNF-α inhibitors,

dimerizing polypeptides including amphiphilic polypeptides, purification polypeptides, stabilizing polypeptides, and targeting polypeptides that are encompassed by the invention. Thus, the scope of the claims includes numerous structural variants, and each genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the claimed genus from others in the amino acid class are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of each genus, and because each genus is highly variant, any RAGE-LBE, any TNF-α inhibitor, any dimerizing polypeptide including any amphiphilic polypeptide, any purification polypeptide, any stabilizing polypeptide, or any targeting polypeptide are insufficient to describe each genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe each genus. Thus, Applicants were not in possession of the claimed genera.

Claims 1, 2, 8-31 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some RAGE-LBE fusion proteins does not reasonably provide enablement for RAGE-LBE fusion proteins comprising any TNF-α inhibitor, any dimerizing polypeptide including any amphiphilic polypeptide, any purification polypeptide, any stabilizing polypeptide, or any targeting polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are directed to a fusion protein comprising a Receptor for Advanced Glycation End Product Ligand Binding Element (RAGE-LBE) and an immunoglobulin element, further comprising a dimerizing polypeptide (including an amphiphilic polypeptide), a purification polypeptide, a stabilizing polypeptide, or a targeting polypeptide, as well as a TNF-α inhibitor, and associated pharmaceutical compositions and protein complexes.

The specification discloses that a Receptor for Advanced Glycation End Products Ligand Binding Element (RAGE-LBE) includes ant extracellular portion of a transmembrane RAGE polypeptide and fragments thereof that retain the ability to bind a RAGE ligand (p.12, lines 10-13). Further, pharmaceutical compositions of the present invention include those that comprise a TNF-α inhibitor selected from the group consisting of a small molecule, an antibody, a peptidomimetic, and a TNFRII-Fc fusion protein (p.5, lines 14-20). Also, etanercept and infliximab are disclosed as anti-TNF agents (p.42, line 4). In addition, the term "dimerizing polypeptide" or "dimerizing

domain" is defined as any polypeptide that forms a dimer or multimer with another polypeptide. A few examples are disclosed, i.e., an amphiphilic polypeptide, an IgG Fc element that forms homomultimers and the Jun and Fos leucine zipper domains that form heteromultimers with each other (p.10, lines 16-25 and p.18, lines 7-16).

Claims 1, 2, 8-31 and 42-44 require the use of several genera of polypeptides. As stated above, Applicants have not described the common features of each genus such that the skilled artisan could identify individual members. The prior art fails to provide compensatory teaching; there are many examples of RAGE-LBE's, TNF-α inhibitors, dimerizing polypeptides, etc. Thus, without further guidance it would require undue experimentation to practice the invention as broadly claimed.

Furthermore, the potential amino acid sequences encompassed by the claims have particular structures and functions, the predictability of which is complex and outside the realm of routine experimentation. Since detailed information regarding the structural requirements of the multitude of potential amino acid sequences encompassed by the claims are lacking, and given the lack of working examples reciting any and all of said sequences, it is unpredictable as to which variations, if any, meet the limitations of the claims.

Accordingly, it is well known in the art that even two polypeptides differing in structure by only one amino acid residue can have completely different functions. For example, Mickle et al. (Med Clin North Am. 2000 May; 84(3): 597-607) teaches that cystic fibrosis (CF) is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance

regulator (CTFR) (p.597). In this polypeptide channel, a mutation of a single glycine to aspartic acid at position 551, gives rise to the CF phenotype. Also, a single phenylalanine deletion at position 508 gives rise to the CF phenotype, thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein.

Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and thus the architecture of an entire cell. For example, Voet et al. (Biochemistry. 1990. John Wiley & Sons, Inc. 126-129 and 228-234) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pp.126-128, section 6-3A and page 230, column 2, first paragraph). Also, Yan et al. (Science 290: 523-527, 2000) teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another. Thus, as outlined *supra*, the predictability of amino acid sequences that would function as claimed is complex and outside the realm of routine experimentation.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to make and use the fusion proteins comprising the plurality

of amino acid sequences encompassed by the claims, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claimed methods, and the breadth of the claims which encompass variant proteins, undue experimentation would be required of the skilled artisan to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 11 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,864,018 to Morser et al (citation AA of Applicant's IDS from 01 March 2004).

The claims are directed to a fusion protein comprising a Receptor for Advanced Glycation End Product Ligand Binding Element (RAGE-LBE) and an immunoglobulin element.

Accordingly, the '018 patent discloses fusion proteins comprising RAGE polypeptides and fragments, including but not limited to ligand binding elements, and an immunoglobulin element (col.7, line 45; col.8, lines 7-14; col.22, line 26-29), thus meeting the limitations of claim 1. The '018 patent also teaches sRAGE (col.4, lines 65-

66), thus meeting the limitation of "extracellular portions of RAGE" in claim 2. Furthermore, the patent discloses one or more amino acid substitutions, insertions, or deletions, i.e. point mutations, which cause altered specificity, enhanced potency, and higher affinity (col.8, line 43 – col.10, line 4), thus meeting the limitations of claim 11. Also, the patent teaches pharmaceutical compositions comprising the polypeptides of the invention and a pharmaceutically acceptable carrier (col.19, lines 21-24; col.20, lines 12-20), thus meeting the limitations of claim 19.

Since the patent discloses all the elements of the claims, claims 1, 2, 11 and 19 are anticipated by U.S. Patent No. 5,864,018 to Morser et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 8-31 and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,864,018 to Morser et al. in view of U.S. 20020102604 to Milne Edwards et al. and as evidenced by WO 94/10308 to Spriggs et al.

The claims are directed to a fusion protein comprising a Receptor for Advanced Glycation End Product Ligand Binding Element (RAGE-LBE) and an immunoglobulin element.

Accordingly, the '018 patent discloses fusion proteins comprising RAGE polypeptides and fragments, including but not limited to ligand binding elements, and an immunoglobulin element (col.7, line 45; col.8, lines 7-14; col.22, line 26-29), as in the instant claim 1. The '018 patent also teaches sRAGE (col.4, lines 65-66), as in claim 2. Furthermore, the patent discloses one or more amino acid substitutions, insertions, or

deletions, i.e. point mutations, which cause altered specificity, enhanced potency, and higher affinity (col.8, line 43 – col.10, line 4), as in claim 11. Also, the patent teaches pharmaceutical compositions comprising the polypeptides of the invention and a pharmaceutically acceptable carrier (col.19, lines 21-24; col.20, lines 12-20), as in claim 19.

The '018 patent does not disclose the Ig's recited by claims 8-10, nor does it disclose the Fc domain recited by claim 13, the heavy chains recited by claims 12 and 14-17 or the polypeptides recited by claims 18-31 and 42-44.

However, the '604 application teaches fusion proteins comprising polypeptides of the invention and functional fragments thereof (paragraphs 0117, 0176 and 0230). The reference also teaches antibodies (including IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE and IgM types) and fragments thereof, (including heavy chains [VH], Fc domains and CH1 domains) as potential partners in the fusion proteins (para. 0364, 0376 and 0377), as in the instant claims 8-10 and 12-15. In addition, the '604 application teaches that the fusions can comprise any combination of the above-mentioned antibody fragments or domains (para. 0376 and 0377), as in claim 16.

Furthermore, the '604 document teaches dimerizing polypeptides, including leucine zippers, as part of the fusions of the invention (para. 0312, 0313, 0314), as in claims 18-20, 27 and 31. Also, at paragraph 314, the '604 application states "examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by

reference." Accordingly, the '308 document teaches jun and fos leucine zippers (p.1, line 34 – p.2, line 2), as in claims 28 and 29.

Additionally, the 604' application teaches stabilizing polypeptides (1260), targeting polypeptides (para. 1679), and purification polypeptides (para. 0176) as part of the fusion proteins of the invention, as in claim 20. The '604 reference also teaches amphiphilic polypeptides and fragments as part of the fusion proteins (para. 1679), as in claim 21, and teaches that fragments of polypeptides can at least 6, at least 8 to 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450 or 500 amino acids (para. 0333), as in claims 22-25. The reference teaches a peptide helix bundle (para. 0671), as in claim 26 and teaches that formation of multimers (i.e., dimerization) can be the result of ionic interaction (i.e., oppositely charged polypeptides bound to each other; para. 0312), as in claim 30. Also, the '604 document teaches protein complexes, comprising a protein of the invention (e.g., para. 0667), as in claim 42. Finally, the '604 document teaches TNF-α inhibitors (e.g., uromodulin) as part of pharmaceutical compositions of the invention (para. 0825), as in claims 43 and 44.

Neither the '018 patent nor the '604 application teach a fusion protein, wherein said immunoglobulin element comprises a CH1 domain of a first immunoglobulin class and a CH1 domain of a second immunoglobulin class, wherein the first and second immunoglobulin classes are not the same. However, in the instant case this is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a

person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal immunoglobulin composition of the fusion protein of claim 17 by varying the immunoglobulin type in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of immunoglobulin type would have been obvious at the time of Applicants' invention.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the RAGE fusion proteins of the Morser et al. patent with the fusion proteins of the Milne Edwards et al. application. The skilled artisan would have been motivated to make these modifications, since both documents teach treatment of Diabetes Mellitus and Alzheimer's disease with the polypeptides of the inventions (co.19, lines 12 and 16 of the '018 patent and para. 1680 and 1801 of the '604 application). The person of ordinary skill in the art would have had a reasonable expectation of success because both documents teach that the fusion proteins would work (entire document).

Conclusion

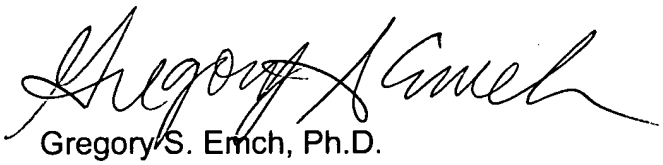
No claims are allowed.

Advisory Information

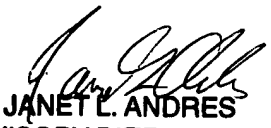
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on Monday through Friday from 9AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
19 September 2006



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